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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,566	06/16/2006	Francis Ignatious	PU60627	7929

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
08/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/596,566	IGNATIOUS ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/12/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on 6/12/2009 in response to the Non-Final Office Action of 12/12/2008 is acknowledged and has been entered.

Claims 1-16 are currently pending.

Claims 13-16 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-12 are under consideration.

The following species are currently under consideration:

-polyethylene glycol as recited in claim 6 for the species election of Claim 5; and

-polylactic acid as recited in claim 9, for the species election of claim 8.

Information Disclosure Statement

The Information Disclosure Statement filed o 6/12/2009 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

New Objections/Rejections Necessitated by Amendment:

Claim Objections

Claim 11 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 11 recites that the bioactive agent is topotecan hydrochloride, which infers that the bioactive agent is a "neutral" salt, topotecan is the cation and Cl is the anion. However, claim 1, from which 11 depends, recites that the bioactive agent is a water soluble cationic bioactive agent which infers that the drug has a positive charge. Thus, in view of topotecan hydrochloride being a neutral species, it is unclear how claim 11 further limits claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, the term "water soluble cationic bioactive agent" in claim 12 is a relative term which renders the claim indefinite. The term "water soluble" when referring to the bioactive agent is not defined by the claim; and the specification does not provide a standard for ascertaining the requisite degree. For example, the solubility of an active agent depends on a variety of factors such as the temperature of the water upon addition of the active agent, e.g., higher water temperature equates to higher solubility, or the amount of the agent to be added to the water. Thus, an agent having a water solubility of less than 10mg/mL may be referred to as a "hydrophobic drug" or "poorly water soluble drug" (see definition of a hydrophobic drug in WO 01/87345, page 7, last paragraph, *of record*), the agents are still soluble in water. Accordingly, a "water soluble" cationic drug as claimed, will be interpreted as any drug which shows some ability to solubilize in water and carries a positive charge, e.g, cationic. See, for example, pages 6, lines 4 to page 7, line 25, for specific examples of therapeutic agents encompassed by the present claims including, but limited to, doxorubicin or cisplatin (claim 10 of the present application).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Seo et al .(WO 01/87345 A1, 2001, *of record*) in view of Cho et al .(WO 2004/022036 A1, 2004, filed on 5/30/2003).

(Note: Due to the indefiniteness set forth above, a "water soluble" cationic drug as claimed, will be interpreted as any drug which shows some ability to solubilize in water and carries a positive charge, e.g, cationic. See, for example, pages 6, lines 4 to page 7, line 25, for specific examples of

therapeutic agents encompassed by the present claims including, but limited to, doxorubicin or cisplatin (claim 10 of the present application).

Seo et al. teach a stable biodegradable polymer micelle-type drug composition which comprises: a modified biodegradable polymeric drug carrier micelle having a hydrophobic drug physically trapped within, wherein the drug carrier comprises an amphiphilic block copolymer having a hydrophilic poly(alkylene glycol) A block component, and a biodegradable hydrophobic polymer B block component selected from the group consisting of poly(lactic acid), poly(glycolic acid) and poly (lactic co-glycolic acid), and wherein the amphiphilic block copolymer has terminal ends modified with end groups that have an attraction or affinity for the hydrophobic drug contained in the micelle core (page 5, lines 7-17). With regards to the hydrophilic poly(alkylene glycol), the WO document teaches that hydrophilic poly(alkylene glycol) include, but are not limited to, polyethylene glycol within the range of 1,000 to 15,000 daltons (page 6, lines 17-23). With regards to the end groups, the WO document teaches that the hydrophobic polymers are capped with an end group such as a benzoyl group (page 9, lines 9-16). With regards to the hydrophobic drug, the WO document teaches that any drug having a water solubility of less than 10mg/mL can be used as a "hydrophilic drug" or poorly water soluble drug" including, but are not limited to, doxorubicin and cisplatin (page 7, line 28 to page 8, line 5).

Seo et al. do not explicitly teach that the hydrophobic polymer comprising a benzoyl end group further comprises a sulfonic acid.

Cho et al. teach amphiphilic block copolymers comprising hydrophobic blocks and hydrophilic blocks, wherein the hydrophobic block comprises a sulfonic acid which enhances the core's affinity to a hydrophobic drug (page 2, line 29 to page 3, line 8).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to modify the hydophobic polymer taught by Seo et al .to further comprise a sulfonic acid in view of the teachings of Cho et al. One would have been motivated to do so because as taught by Cho et al .the addition of sulfonic acid to hydrophobic block polymers enhances the core's affinity to water-insoluble drugs. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the hydophobic polymer taught by Seo et al .to further comprise a sulfonic acid in view of the teachings of Cho et al, one would further enhance the affinity to hydrophobic drugs.

Note: In order to expedite prosecution, the Examiner would like to respond to Applicants arguments to the previous rejection as they relate to the present rejection. In response to this rejection, Applicants contend that the present invention is directed to polymeric micelle complexes of water soluble bioactive agents (drugs, diagnostics agents, ect.), specifically water soluble, cationic bioactive agents. Accordingly, Applicants assert that the polymer allegedly taught by Seo to comprise a sulfonic acid group allegedly taught by Cho would enhance "the core's affinity to water insoluble drugs" fail to render the present invention patentable.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants arguments, the Examiner acknowledges that the combination of Seo and Cho are directed to hydrophobic or poorly water soluble drugs. However, the Examiner recognizes that due to the indefiniteness as set forth above, a "water soluble" cationic drug as claimed, will be interpreted as any drug which shows some ability to solubilize in water and carries a positive charge, e.g, cationic. See, for example, pages 6, lines 4 to page 7, line 25, for specific examples of therapeutic agents encompassed by the present claims including, but limited to, doxorubicin or cisplatin (claim 10 of the present application). Accordingly, Seo et al. teaching of poorly water soluble drugs such as doxorubin (claimed in Claim 10 of the current Application as being a water soluble cationic bioactive agent) meets the claimed limitation.

Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seo et al .(WO 01/87345 A1, 2001, of recrod) in view of Cho et al .(WO 2004/022036 A1, 2004, filed on 5/30/2003, of record), as applied to claim 1-10, in further view of Giovanella et al. (2002/0107260, 2002, of record) and Grochow et al .(Drug Metabolism and Disposition 1992; 20: 706-713) .

Seo et al. in view of Cho et al .teach a stable biodegradable polymer micelle-type drug composition which comprises: a modified biodegradable polymeric drug carrier micelle having a hydrophobic drug physically trapped within, wherein the drug carrier comprises an amphiphilic block copolymer having a hydrophilic poly(alkylene glycol) A block component, and a biodegradable hydrophobic polymer B block component selected from the group consisting of poly(lactic acid), poly(glycolic acid) and poly (lactic co-glycolic acid), and wherein the amphiphilic block copolymer has terminal ends modified with an end group comprising a benzoyl sulfonic acid. With regards to the hydrophobic drug, the WO document teaches that hydrophobic drugs include, but are not

limited to, doxorubicin and cisplatin (page 8, lines 2-5 of Seo et al.). Moreover, Seo et al. teach that the biodegradable polymer micelle-type drug composition has minimal side effects and shows improved bioavailability (abstract).

Seo et al. in view of Cho et al .do not explicitly teach that the hydrophobic drug is topotecan or a a method of treating cancer comprising administering an effective amount of the complex to a patient in need thereof.

Giovanella et al. teach a method of treating a tumor in a mammal comprising administering to said mammal a water-insoluble compound, wherein the water-insoluble compound includes, but is not limited to topotecan (claim 1 of the publication). Cho et al. teach amphiphilic block copolymers comprising hydrophobic blocks and hydrophilic blocks, wherein the hydrophobic block comprises a sulfonic acid which enhances the core's affinity to a water-insoluble drug (page 2, line 29 to page 3, line 8).

Grochow et al. teach that topotecan is commercially available from the National Cancer Institute as the hydrochloride salt (page 707, 1st column, Formulation and Dosage).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to substitute the hydrophobic drugs as taught by Seo et al .in view of Cho et al .for topotecan in view of the teachings of Giovanella et al. One would have been motivated to do so because as taught by Giovanella et al., topotecan is a water-insoluble drug. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting the hydrophobic drugs as taught by Seo et al .in view of Cho et al .for topotecan in view of the teachings of Giovanella et al., one would achieve a suitable delivery means for water-insoluble topotecan. Similarly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use topotecan hydrochloride since it has been shown to be commercially available in view of the teachings of Grochow.

Additionally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the biodegradable polymer micelle-type drug composition as taught by Seo et al .in view of Cho et al .to a patient suffering from cancer in view fo the teachings of Giovanella et al. One would have been motivated to do so because as taught by Seo et al., the biodegradable polymer micelle-type drug composition comprising chemotherapeutic agents has minimal side effects and shows improved bioavailability Thus, one of ordinary skill in the

art would have a reasonable expectation of success that by administering the biodegradable polymer micelle-type drug composition as taught by Seo et al .in view of Cho et al .to a patient suffering from cancer in view of the teachings of Giovanella et al., one would achieve improved bioavailability of the drug.

Therefore, NO claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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